THERAPY AND PREVENTION
CORONARY ARTERY DISEASE

Comparison of the antianginal effectiveness of nifedipine, verapamil, and isosorbide dinitrate in patients receiving propranolol: a double-blind study

MAYER M. BASSAN, M.D., DANIEL WEILER-RAVELL, M.D., AND ODED SHALEY, M.D.

ABSTRACT Ten men with stable angina not fully relieved by optimal doses of propranolol were given on each of four mornings a single dose of 10 mg nifedipine, 120 mg verapamil, isosorbide dinitrate (5 to 30 mg, previously titrated to lower systolic blood pressure by 15 to 20 mm Hg), or placebo, in double-blind fashion. Bicycle exercise to angina was performed hourly for 8 hr thereafter. All three vasodilators increased exercise time by at least 50% by the first hour (p < .001), with a gradually diminishing effect persisting for 6 to 8 hr (p < .01). Although for the group there were no differences in magnitude and duration of effect among the three drugs, in five of the individual patients there were important differences in response favoring one or another vasodilator. We conclude that nifedipine, verapamil, and isosorbide dinitrate are equally effective and reasonably long-acting antianginal supplements to propranolol, although some patients may benefit more from one than another of the three.


ALTHOUGH β BLOCKERS are usually prescribed for patients with angina pectoris and are generally effective in improving exercise tolerance, the improvement is frequently only partial, in which case a second drug will often be added to the therapeutic regimen. Results of many recent studies leave no doubt that oral isosorbide dinitrate (ISDN) is both an effective and a reasonably long-acting antianginal drug. The relatively new calcium-blocker vasodilators verapamil and nifedipine are gaining increasing popularity as antianginal drugs based on a large number of well-performed double-blind, randomized, controlled trials. The combination of a β-blocker with a vasodilator (usually one of the long-acting nitrates) to achieve maximal symptomatic improvement in chronic angina pectoris has seemed logical and has been accepted for many years. Previous studies have demonstrated that ISDN, nifedipine, and verapamil are all effective antianginal supplements to the β-blocker propranolol. The present study was undertaken in order to ascertain the relative supplemental antianginal effectiveness of the three above-mentioned vasodilators in patients who continue to suffer from angina pectoris despite optimal doses of propranolol.

Patients and methods

Patients. Ten men with classic exertional angina pectoris were studied. In addition to reproducible provocation of typical anginal pain during bicycle exercise, one or more objective indicators of ischemic heart disease was present in each patient (table 1). None of the patients had hypertension or evidence of congestive heart failure. Eight patients had undergone cardiac catheterization (with the coronary artery findings as described in table 1), and none showed abnormal global left ventricular function. None of the 10 patients had been treated with nifedipine or verapamil. Five patients had been treated with ISDN.

Training. The patients were trained on a bicycle ergometer according to the exercise protocol of Redwood et al. in which the work level is increased by 20 W every 3 min and the starting level is chosen so that angina is precipitated between the third and sixth minutes of exercise. Training to the point of stable performance (appearance of angina at a constant time ± 30 sec) required at least 10 and usually 15 to 20 exercise bouts to angina.

β-Blocker therapy. Eight of the 10 patients were already receiving propranolol before becoming candidates for the study. In five of these patients there had been some subjective clinical improvement from the drug, and the commonly accepted clinical criteria for effective β-blocker therapy of resting pulse in the range of 55 to 60 beats/min and heart rate during exercise to angina not exceeding 100 beats/min were fulfilled. The other five patients were treated with progressively increasing doses of propranolol. Each exhibited some improvement in bicycle exercise time and the final dose of propranolol was selected after a higher dose was shown to be no more effective. The daily dose of propranolol for each patient is listed in table 1; the mean daily dose was 218 mg. Clinical and bicycle exercise-induced angina

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Received Jan. 21, 1983; revision accepted May 19, 1983.
pectoris continued to be present in all patients despite β-blocker therapy.

ISDN. During the training phase each patient was given test doses of ISDN to eliminate patients with nitrate-induce headache and to determine the dose that would cause a 15 to 20 mm Hg drop in systolic blood pressure 1 hr after drug administration. The doses finally selected for use in the study are listed in table 1; the mean dose was 17 mg.

Study design. The study was carried out over 4 separate days. The patients reported to the exercise laboratory at 8 A.M., 1 hr after having taken their usual morning dose of propranolol. After a 30 min rest they performed a control exercise bout, beginning at the starting work level established during the training phase (table 1) and continuing to the point of angina. They were then given a capsule that contained a placebo, 10 mg of nifedipine, 120 mg of verapamil, or the previously determined dose of ISDN. Dispensing order of the placebo and active drugs on the 4 days was random and double blind. The patient then exercised to angina or extreme leg fatigue once hourly for 8 hr after drug administration.

In five of the 10 patients the 4 test days were consecutive. In four other patients the study was carried out over periods of 8, 10, 14, and 16 days. In one patient the study period extended over 6 weeks. None of the five patients in whom the test days were nonconsecutive received any exercise training between test days. The order of drug administration is indicated in table 1.

A modified lead V5 of the electrocardiogram (ECG) was monitored continuously. Resting heart rate and blood pressure were recorded after the patient had been sitting on the bicycle for 5 min. Special care was taken in determining resting blood pressure, and a minimum of three measurements with a wall-mounted mercury sphygmomanometer were taken to ensure that an accurate and stable value was recorded. The patient pedaled at a constant rate of 50 rpm and signaled the onset of angina. He then continued pedaling for 15 to 20 sec while an ECG strip and blood pressure were recorded at peak exercise. In those exercise bouts in which patients were not limited by chest pain, they were encouraged to exert maximal effort. When fatigue was the reason for stopping, it was noted whether the fatigue was accompanied by significant ST depression or followed by pain, the onset of which was in the early recovery phase.

Exercise laboratory temperature was kept constant at 23 ± 1°C. Two patients smoked occasionally, but not on test days. Aside from propranolol only patients 1 and 4 were receiving any medication; these two were receiving long-term therapy with oral ISDN. On the study days the morning dose was omitted so that neither patient had received this drug within 12 hr of the test procedure. Seven of the 10 patients were not bothered by hunger and completed the 8½ hr procedure with drinking water only. The other three patients had a light snack on all days after the fifth hour’s exercise. All of the exercise tests in an individual patient were performed by one of two physicians who were involved with the patient from the training phase.

The degree of physician blinding was only partial because of marked differences in exercise performance of patients on placebo and active drug; this became obvious in most patients by the first or second hour exercise bout. Nevertheless, although the investigator usually knew when an active drug had been given, he did not know which of the three vasodilators it was.

The research nature of the study was explained to each patient and appropriate informed consent was obtained. The study protocol was approved by the hospital committee for research involving human subjects. The study was performed without drug company assistance.

The differences between the effects of placebo, nifedipine, verapamil, and ISDN were analyzed by an additive two-way analysis of variance with time and individual patients as factors. The significance of the differences at each hour was tested by the appropriate two-tailed t test. All means are expressed ± SE.

### TABLE 1

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (yr)</th>
<th>Coronary angio.</th>
<th>Previous ischemic event</th>
<th>Stress test ST ↓ (mm)</th>
<th>Propranolol daily dose (mg)</th>
<th>ISDN dose (mg)</th>
<th>Order of drug administration</th>
<th>Starting exercise level (W)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56</td>
<td>100% LAD</td>
<td>Al</td>
<td>1½</td>
<td>160</td>
<td>30*</td>
<td>I-P-V-N</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>100% LAD</td>
<td>MI</td>
<td>1</td>
<td>160</td>
<td>20</td>
<td>V-N-P-I</td>
<td>60</td>
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<tr>
<td>3</td>
<td>43</td>
<td>100% LAD</td>
<td>None</td>
<td>3</td>
<td>240</td>
<td>5</td>
<td>N-I-V-P</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>37</td>
<td>100% RCA</td>
<td>MI</td>
<td>2</td>
<td>120</td>
<td>30*</td>
<td>P-I-N-V</td>
<td>40</td>
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<tr>
<td>5</td>
<td>67</td>
<td>Not done</td>
<td>None</td>
<td>4</td>
<td>120</td>
<td>10</td>
<td>P-N-I-V</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>62</td>
<td>90% LAD</td>
<td>MI</td>
<td>2</td>
<td>60</td>
<td>10</td>
<td>N-P-V-V</td>
<td>60</td>
</tr>
<tr>
<td>7</td>
<td>43</td>
<td>100% LAD</td>
<td>Al</td>
<td>1½</td>
<td>360</td>
<td>15</td>
<td>I-V-P-N</td>
<td>80</td>
</tr>
<tr>
<td>8*</td>
<td>58</td>
<td>100% LAD</td>
<td>Al</td>
<td>None</td>
<td>360</td>
<td>15</td>
<td>V-N-P-I</td>
<td>40</td>
</tr>
<tr>
<td>9</td>
<td>55</td>
<td>Not done</td>
<td>MI</td>
<td>1½</td>
<td>240</td>
<td>15</td>
<td>V-P-N-I</td>
<td>90</td>
</tr>
<tr>
<td>10</td>
<td>42</td>
<td>100% LAD</td>
<td>None</td>
<td>1</td>
<td>360</td>
<td>15</td>
<td>P-V-I-N</td>
<td>110</td>
</tr>
</tbody>
</table>

AI = acute ischemia (chest pain with transient T wave inversion but no enzyme rise); MI = myocardial infarction; I = ISDN; N = nifedipine; P = placebo; V = verapamil.

*Long-term ISDN therapy.

*After coronary bypass surgery.
TABLE 2
Mean duration of exercise in seconds (± SE) for control and the hourly exercise bouts after placebo, nifedipine, verapamil, and ISDN

<table>
<thead>
<tr>
<th>Drug</th>
<th>Control</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
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<tr>
<td>Placebo</td>
<td>255±16</td>
<td>247±15</td>
<td>243±16</td>
<td>242±17</td>
<td>245±17</td>
<td>234±15</td>
<td>217±15</td>
<td>222±15</td>
<td>221±15</td>
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<tr>
<td>Nifedipine</td>
<td>240±17</td>
<td>372±21</td>
<td>392±22</td>
<td>368±27</td>
<td>354±25</td>
<td>331±28</td>
<td>301±28</td>
<td>287±29</td>
<td>277±26</td>
</tr>
<tr>
<td>Verapamil</td>
<td>247±15</td>
<td>363±24</td>
<td>362±21</td>
<td>366±26</td>
<td>349±29</td>
<td>329±27</td>
<td>288±24</td>
<td>272±28</td>
<td>274±29</td>
</tr>
<tr>
<td>ISDN</td>
<td>252±18</td>
<td>423±39</td>
<td>398±18</td>
<td>369±17</td>
<td>351±22</td>
<td>322±24</td>
<td>285±27</td>
<td>243±26</td>
<td>244±26</td>
</tr>
</tbody>
</table>

^A Drug compared with placebo at same hour.

Results

Exercise time to angina

Group performance (Table 2 and Figure 1). Exercise time to angina after placebo was relatively constant over the 8 hr observation period. Each of the three drugs caused a marked increase in mean exercise duration by 1 hr after administration (p < .001). Although the increase was somewhat greater after ISDN the differences among the drugs was not statistically significant. Similarly, each of the drugs was superior to placebo to a similar degree through the sixth hour. While nifedipine and verapamil were superior to placebo through the eighth hour, the antianginal effect was markedly reduced and the difference between them and ISDN was not significant.

Individual performance. Figure 2 depicts the patterns of response for each of the 10 patients. It indicates when patients were stopped by fatigue (with or without evidence of ischemia) rather than angina. Patient 8 developed a severe headache after nifedipine and was unable to exercise beyond the fourth hour on that day. Patients 1, 4, and 5 performed a single exercise test at 7 1/2 hr and this value was used for both the seventh and eighth hour values. Patient 5 developed hypotension and was unable to exercise at the first hour after ISDN.

Although for the group as a whole there was little difference among the drugs with regard to onset, cessation, or magnitude of effect, this was true for only a minority of the 10 individual patients. In patients 1 and 5, as well as 8 (who responded to none of the three
In five patients there were marked differences favoring one or two of the drugs that would be likely to be of clinical significance. In patient 2 the peak effect from hours 2 to 4 was greater for nifedipine than for verapamil or ISDN. In patient 3 the effects of nifedipine and ISDN were considerably greater than those of verapamil throughout most of the period of drug action. ISDN was markedly superior to nifedipine and verapamil in magnitude and duration of effect in patient 4. Verapamil and nifedipine had a longer duration of action than ISDN in patient 9, and in patient 10 the effect of verapamil was much more prolonged than that of nifedipine or ISDN. Thus, while no one drug was clearly superior to the others for the group or in more of the patients, half of the patients did have a better (or worse) response to one of the drugs compared with the other two.

Improvement in exercise tolerance after active drugs was indicated not only by the delayed appearance of the subjective sensation of angina but also, in those patients who developed ST depression before angina, by a marked delay in the development of the ECG changes. Figure 3 depicts the electrocardiographic confirmation of reduced myocardial ischemia in patient 3 and demonstrates that the phenomenon was common to all three drugs.

**Blood pressure** (figure 4). Each of the three drugs caused a marked drop in seated resting systolic blood pressure within 1 hr after its administration (p < .002 for each drug). The reduction was greatest after ISDN (−26 mm Hg, p < .001 compared with nifedipine and verapamil). The fall in blood pressure was significant through the eighth hour in the case of nifedipine (p < .03), through the seventh hour for ISDN (p < .003), and lasted through the fifth hour for verapamil (p < .03).

The effect of the drugs on blood pressure during exercise was examined by comparing the value at the

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**FIGURE 2.** Comparison of the individual responses to nifedipine, verapamil, ISDN, and placebo in the 10 patients. Each point denotes the duration of a single exercise bout and the symbol indicates the reason for stopping. Nearly identical responses to all drugs were seen in patients 1, 5, and 8. Slight differences were seen in patients 6 and 7, while considerable differences likely to be of clinical significance were seen in patients 2, 3, 4, 9, and 10.
hour the drug exerted its maximum effect on exercise tolerance with the parallel value in each patient during exercise after placebo. At submaximal (3 min) exercise, all three drugs caused a significant fall in blood pressure (verapamil, \(-13\) mm Hg, \(p < .002\); nifedipine, \(-9\) mm Hg, \(p < .05\); ISDN \(-8\) mm Hg, \(p < .04\)). At peak exercise (angina or fatigue) there was no significant difference in blood pressure in patients on placebo and any of the three drugs, although a higher workload was almost always achieved after drug administration.

Heart rate. Control mean seated resting heart rate was 58 beats/min, and peak heart rate was 92 beats/min, indicating a good degree of \(\beta\)-blockade. Vasodi-
lator-induced changes in heart rate were minimal (probably due to the concomitant high degree of β-blockade). After verapamil there was no difference in resting or exercise heart rates compared with after placebo at any hour. After nifedipine and ISDN there were transient slight increases in heart rates compared with after placebo, but these were seen only at rest at the first hour after drug administration (nifedipine, +6 beats/min, p < .01; ISDN, +6 beats/min, p < .03).

Rate-pressure product (RPP). Figure 5 depicts the changes in the product of heart rate and systolic blood pressure for the group at the hour of best individual exercise performance after drug administration compared with the RPP at the same hour after placebo. Each drug caused a significant fall in RPP at rest and at submaximal exercise (3 min) due to the fall in blood pressure. There was no significant difference in RPPs after any of the drugs and placebo at peak exercise (angina or fatigue), although in almost every patient a higher workload was performed at peak exercise after active drug administration.

Adverse effects. In patient 5 the systolic blood pressure fell to 60 mm Hg while he was seated on the bicycle 1 hr after 10 mg of ISDN. He complained of light-headedness and was unable to exercise. The hypotension subsided by the second hour. Patient 8 developed a severe headache after nifedipine and was unable to exercise beyond the fourth hour. This patient also developed a mild headache after ISDN. There were no symptomatic side effects after verapamil. Patient 10 had a slight prolongation of the PR interval from 0.18 to 0.21 sec and this lasted for 3 hr after verapamil administration.

Discussion

Our results indicate a marked increase in exercise tolerance in "β-blocked" angina patients after oral administration of a single dose of nifedipine, verapamil, or ISDN. We found a rapid onset of action, generally within 1 hr, and a mean duration of near-maximum effect of 4 to 5 hr after drug administration. These data are compatible with pharmacologic study results showing rapid and complete absorption of each of the drugs after oral administration, with a plasma half-life of approximately 4 hr for nifedipine and verapamil, and 2 to 3 hr for ISDN.
The duration of action of the antianginal effect of an individual drug was quite variable from patient to patient, ranging from 3 to 8 hr, and there was generally considerable diminution of the beneficial effect in the later hours even in the patients in whom there was a long duration of action. Thus, our results suggest that these vasodilators should usually be administered at least every 6 hr in order to maintain continuous maximum benefit. It must be realized, however, that the possibilities of drug tolerance and/or accumulation may limit the application of our findings after single-dose drug administration to the clinical situation of long-term therapy.

In comparing the antianginal effectiveness of the three drugs, our data suggest that no one drug is clearly superior to the others. Patients responding to one of the drugs will respond to the others, although there are often differences in the magnitude, onset, and duration of effect. In a significant percentage of patients, these differences can be expected to be of clinical importance, although we know of no way of predicting which patient is likely to benefit more from which drug.

The question may be raised as to whether the doses of the three different vasodilator drugs were equally optimal. As a result of the titration procedure, the dose of ISDN was probably maximal for each patient. It is possible that had a similar blood pressure–lowering titration been performed for verapamil and nifedipine, the improvement in exercise tolerance would have been greater after their administration. There are, however, no generally accepted methods for titrating the antianginal doses of verapamil or nifedipine, except possibly by exercise testing itself. Since we did not use exercise performance in the titration for ISDN, doing so for the other drugs would have selectively eliminated nonresponders from the study, and in addition would have made the investigation very difficult to perform. Titration according to blood pressure lowering would have been easier, but would also have rendered the protocol exceedingly cumbersome.

Nevertheless, the doses of verapamil and nifedipine were probably at least close to optimal. The 120 mg dose of verapamil is on the high side of doses found to be effective, and is the one most commonly used in placebo-controlled studies.5–8, 18, 19 Ten milligrams is a frequently used dose of nifedipine, and the mean fall in blood pressure of 18 mm Hg we achieved suggests that the dose was close to maximal. Moskowitz et al., 9 Guiney et al., 28 and Prempree et al. 29 compared 10 and 20 mg doses of nifedipine and found little if any additional benefit from the larger dose.

If the antianginal effectiveness of verapamil, nifedipine, and ISDN as supplements to β-blockade are approximately equal, on what basis might the clinician exercise an initial preference in an individual patient? In terms of cost and patient-years of experience, the choice would clearly be in favor of ISDN. Although none of our patients demonstrated any acute adverse effects from the verapamil-propranolol combination, and our experience and that of others18, 19 has shown the combination to be safe in the overwhelming majority of patients, the occasional and anecdotal reports of cardiovascular catastrophe after administration of verapamil in β-blocked patients gives basis for caution. Therefore, our current practice is to add verapamil to propranolol only after ISDN and nifedipine have proved insufficiently effective or have caused intolerable side effects.

The effectiveness and side effects of the different drugs can only be assessed after a trial in the individual patient. In our experience headache, which so often precludes use of ISDN, is less of a problem with nifedipine and nonexistent with verapamil. Many patients receiving nifedipine are bothered by ankle edema, but we have observed this only once from verapamil.

Regarding the mechanism of action of the three vasodilators, our observations are limited by the fact that all our patients were receiving propranolol. All the drugs lowered the RPP at rest and at submaximal exercise, while at peak symptom-limited exercise, the greater amount of exercise the drugs permitted occurred at an RPP no different from that achieved after placebo. These findings are compatible with a predominantly peripheral mechanism of action (i.e., reduced O2 demand due to lowered blood pressure), which has been proposed for each of the three drugs.30, 32 Nevertheless, since we feel that the RPP estimation of myocardial oxygen demand does not necessarily take into account all the relevant determinants, we cannot rule out a direct coronary mechanism due to vasodilation of even diseased coronary arteries and increased coronary blood flow.33–35 a change in myocardial metabolism in the case of nifedipine36 or verapamil,37 or a preferential redistribution of blood flow to ischemic areas in the case of ISDN.38

We are most indebted to Ms. Esther Bachar-Bassan for the statistical evaluations.

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CIRCULATION
Comparison of the antianginal effectiveness of nifedipine, verapamil, and isosorbide dinitrate in patients receiving propranolol: a double-blind study.
M M Bassan, D Weiler-Ravell and O Shalev

Circulation. 1983;68:568-575
doi: 10.1161/01.CIR.68.3.568
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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